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# Peptide Product Development Challenges: API Sameness

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## FDA Expectations:

- Comparative characterization studies to support active ingredient sameness, impurity assessment, and waiver request for in vivo bioequivalence study requirements
  - Primary sequence confirmation (API)
  - Physicochemical characterization (API)
  - Impurity profiling (API and peptide related)
  - Comparative high-order structure assessment (where applicable)
  - Comparative aggregation/oligomer evaluation
  - Biological activity comparison (where appropriate)
- FDA's product-specific guidance may impose additional sameness characterization expectations beyond the general guidance.

## Applicable Guidance:

- Product-Specific Guidance for Generic Drug Development
- ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021) Withdrawn on 07/28/2026
- Sameness Evaluations in an ANDA — Active Ingredients (November 2022 Draft Guidance)

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## Industry Challenges

- **RLD age in characterization challenges**
  - In some cases, FDA recommends, “no less than three batches of the RLD aged prior to expiry” which may be a challenge, industry can’t always obtain appropriately aged RLD samples, particularly for beginning-of-shelf-life comparisons.
  - Given the lengthy timelines for some characterization studies, additional clarity on FDA expectations for sample age matching and the definition of beginning versus end of shelf life would be valuable, what would be an acceptable difference?
- **Data Variability between Test and Reference**
  - Establishing the acceptable variation between Test and Reference for characterization testing and impurity profile comparability
  - Impurity profiles between Test and Reference may be different due to manufacturing process therefore how to support sameness without a clinical or immunogenicity study
- **Method Variability**
  - When biologic activity is a required comparative characterization analysis, this method may not be sensitive to detect (minor) differences relevant to peptide sameness assessments
  - Method-dependent differences in impurity detection, identification, and quantification can complicate interpretation of peptide comparability assessments
- **PSG Revision Timing**
  - Draft PSGs may be revised during development, potentially introducing new studies, batches, time points, or analytical expectations after characterization activities have started.
- **FDA Expectations Uncertainty**
  - Due to peptide complexity and product to product specifics the requirements can vary therefore this can be a challenge to set up peptide development programs. “Biological and functional assays (e.g., enzymatic, ligand binding, or cell based) are not always needed.”

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## Considerations

- Per FDA Guidance: Controlled Correspondence, pre-ANDA Development Meeting, or Post PSG Meeting to obtained FDA agreement on strategy, however timing can limit options for obtaining FDA feedback
- Define the criteria used by FDA to determine peptide characterization requirements and acceptable parameters supporting API sameness assessments.
- Define allowable difference in RLD and Test data
- Update Peptide Guidance with details on these items and include general parameters for comparative characterization studies to support active ingredient sameness, impurity assessment, and waiver request for in vivo bioequivalence study requirements

## Helpful FDA Updates

- FDA updated guidance regarding the Active ingredient-related impurity comparisons in multiple PSGs,
  - Clear specifications for impurities, although FDA may request to tighten during review
  - Reduce the RTR risk that was previously considered due prior FDA guidance.